PDA Training Course Extractables & Leachables

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# United States Pharmacopeia:
## USP Chapters Addressing Extractables/Leachables from Packaging and Manufacturing Systems

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# Trainer

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- 30 + years of experience in chemical characterization (E&L) of pharmaceutical packaging, manufacturing systems and medical devices, largely spent at Baxter Healthcare.
- Nearly 170 journal articles, numerous book chapters and one book on the topics of analytical chemistry, ion chromatography, theory and practice of chemical characterization.
- If there is something that you do not like about an E&L Standard, Monograph or Recommendation, then chances I am probably to blame.

# Training Outline

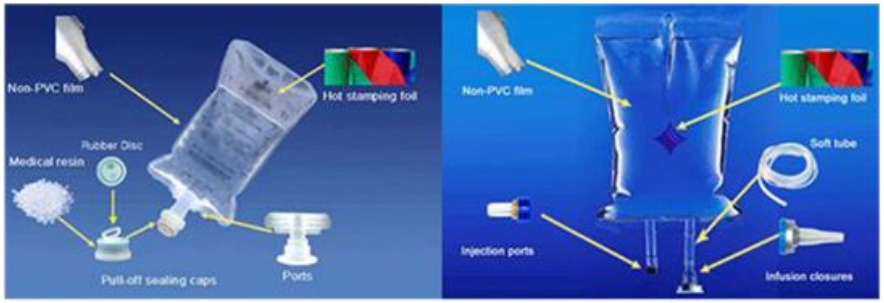
1. The USP Approach to Pharmaceutical Materials.
2. Chapters <381>, <1381>, <382> and <1382> for *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems.*
3. Chapters <661.1> and <1661> for *Plastic Materials of Construction**.
4. Chapter <661.2> and <1661> for *Plastic Packaging Systems for Pharmaceutical Use.*
5. Chapters <1663> and <1664>, Extractables and Leachables.
6. Chapters <665> and <1665> for *Polymeric Materials, Components and Systems used in the Manufacturing ….*

* for Packaging Systems

# The USP Philosophy

Ingredients → Extractables → Leachables

Materials → Systems → Packaged Products




# The Universe of USP E&L Chapters

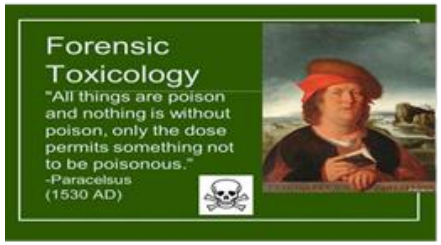
**<1663>, Extractables**

**<1664>, Leachables**

- 1664.1 OINDP
- 1664.X Other Dosage Forms

**USP <381>**

**Biological Assessment:**
USP <87>, <88>, <1031>





**USP <661>**

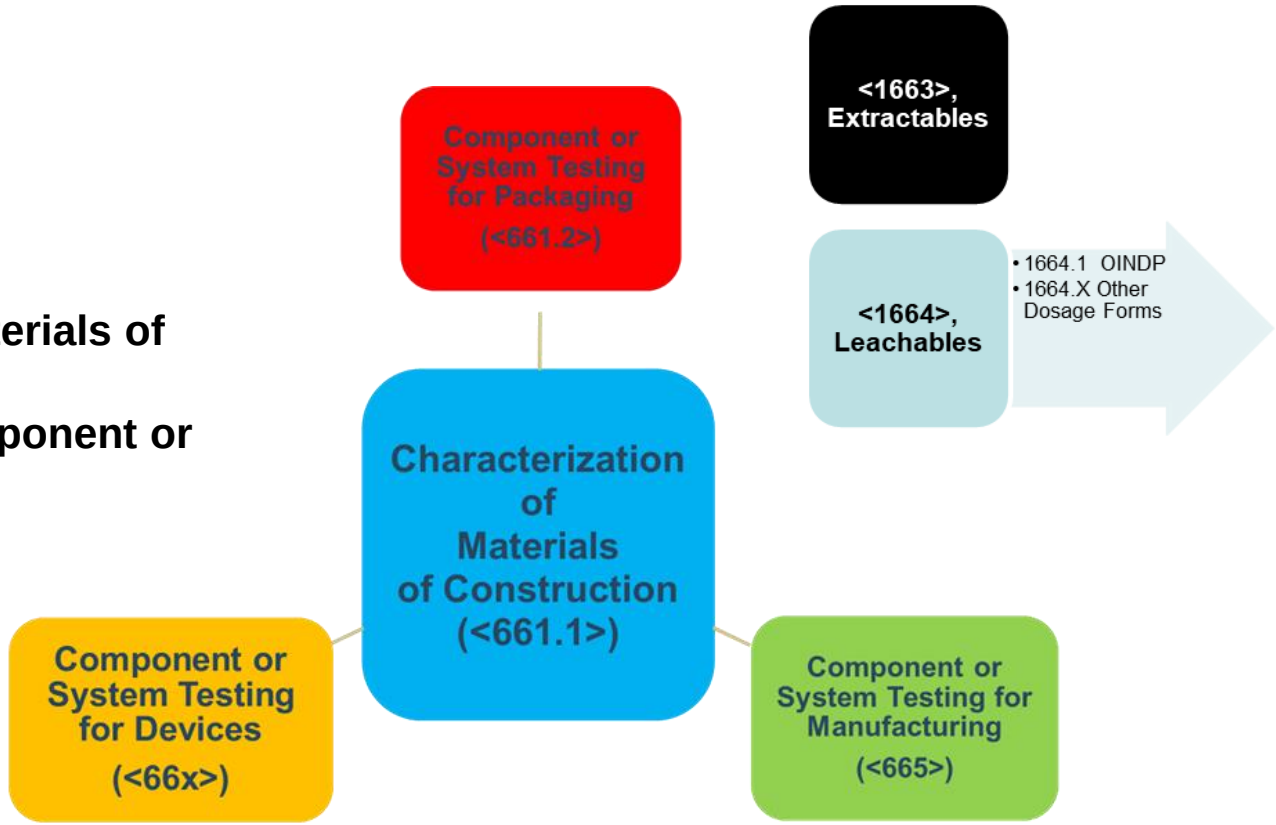



**USP <662>**

**USP <660>**

# The USP Approach to Plastics

- **Standardize at the Materials of Construction level**
- **Customize at the Component or System level**



# Underlying Principles

- **Risk-based approach** – amount and degree of testing reflects the level of risk.
- **Low risk is not no risk**.
- **"Aim for the Middle"** – information generated is directly applicable in many situations and appropriately applicable in extreme situations.
- **"Minimum Standard"** – the "minimum standard" established by the USP is a baseline applicable for all situations which may need to be augmented in "special cases".
- **Relevant information drives good decisions making**.
- **Materials of construction are tested** for the purpose of **selection.**
- **Components are tested for selection and/or qualification.**
- **Testing for selection and testing for qualification are different by necessity and purpose.**

# Elastomeric Closures for Injection

- **Chemical Assessment:**
  - **<381> ELASTOMERIC COMPONENTS IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
  - **<1381> ASSESSEMENT OF ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
- **Functional Assessment:**
  - **⟨382⟩ ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
  - **⟨1382⟩ ASSESSMENT OF ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**

# Contents of <381>



**Extractable elements: It is the component user's responsibility to evaluate the need for extractable elements** testing and, if such testing is necessary, **to establish and justify the means by which testing is accomplished**, taking into account extraction conditions, target elements and reporting requirement.

# Key Points in <381>

1. Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven safe and compatible for its intended use.

2. The chapter provides baseline requirements for the selection of elastomeric components to be further qualified for use in a given system.

3. The chemical testing prescribed is orthogonal:
   - the physicochemical tests provide a general overview of extracted chemicals,
   - the extractable elements test, if performed, provides a quantitative assessment of potential elements of concern,
   - Because chemical testing alone may not be adequate, it is augmented by establishing biological reactivity.

4. If components comply with the <381>requirements, studies should then be designed to determine safety and compatibility as recommended in Assessment of Extractables Associated with Pharmaceutical Packaging - Delivery Systems ⟨1663⟩ and Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging - Delivery Systems ⟨1664⟩.

# Key Points in <381>

5. Two types: Type 1 meets all the requirements; Type 2, which may be necessary for functional reasons, do not necessarily meet Appearance, Absorbance and Reducing Substances.

6. Type I and Type II closures must both conform to the requirements of either the USP in vitro <87> or the in vivo < 88> biological reactivity tests.

7. Physicochemical Tests are based on: a water extraction:
   - Extraction with Water,
   - Autoclaved extraction (121˚ C for 30 min),
   - 2 mL/cm$^2$

8. Tests are always conducted on the components after surface modifications.

9. The tested components need to be representative of the final components as intended for use in a packaging or delivery system.

10. Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.

# Physicochemical Tests in <381>

**Determination of turbidity (opalescence):** a nonspecific test for all the extractable species in a rubber formulation that are not soluble in an aqueous solution. A high turbidity is the indication of a high extractable potential.

**Acidity/alkalinity:** a nonspecific test indicative of the acidic, basic, or buffering power of the aqueous extractables from the rubber formulation. High values in the acidity/alkalinity test may need to be evaluated in conjunction with drug product's pH.

**Color:** a nonspecific test indicative of the presence of extractable species in a rubber formulation that have the capacity of attributing color to an aqueous solution.

**Absorbance:** The UV spectrum of an aqueous extract from a rubber formulation is indicative of the unsaturated or aromatic character of the chemical species extracted such as antioxidants, preservatives, and curing or dying agents.

**Reducing substances:** a nonspecific test for extracted species from a rubber formulation with potential reducing power (polymer, curing system, preservatives, antioxidants, etc.).

**Ammonium and Volatile Sulfides:** specific tests for curing-related extractables. Ammonium ions can be generated during the curing process. Sulfur and sulfur precursors are often used as components of curing systems.

# Status of Elastomers Chapters

1. <381>:  Official as of 1-Dec-2020
2. <382>:  Published in USP43/NF38, 2nd Supplement. To be official 1-Dec-2025
3. <1381> and <1382>:  Official as of 1-Dec-2020


# Plastic Packaging and Materials

## USP <661>, Current

### PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

**Tests and Specifications for:**

- Polyethylene Containers
- Polypropylene Containers
- Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Containers

**Tests include:**

- Identity
- Physicochemical Properties of a Water Extract
  - Non-volatile Residue
  - Residue on Ignition
  - Heavy Metals
  - Buffering Capacity


**Official as of 1-Nov-2020**

# Plastic Packaging and Materials

## USP <661> (and related), Future

***<661> Plastic Packaging Systems and their Materials of Construction***

***<661.1>***
**Plastic Materials of Construction**

*(Materials Characterization)*

- Identification
- Biological Activity
- Physicochemical Tests
- Extractable Metals (as appropriate)
- Plastic Additives

***<661.2>***
**Plastic Packaging Systems for Pharmaceutical Use**

*(Systems Characterization)*

- Biological Activity
- Physicochemical Tests
- Safety Assessment (Extractables/Leachables)

**Future**

**Official as of 1-Dec-2025 with early adoption option**

6

# Plastics Chapters in 2025

- **Monograph <661>** is an introductory Monograph that establishes the Scope of the Packaging Monographs, and their inter-relationships. The <661> Monograph also establishes the relationship between the packaging Monographs and other USP chapters such as <1663> and <1664>.
- **Monograph <661.1>** provides test methods and specifications for **Plastic Materials of Construction**.
- **Monograph <661.2>** provides test methods and specifications for **Plastic Packaging Systems for Pharmaceutical Use**.
- **Monograph <1661>** provides insights into the science and technology of <661.1> and <661.2> and serves as a **"user's manual"** for both <661.1> and <661.2>.
- **Monographs <1663>** and **<1664>** provide insights and **recommended practices** on how to design and perform **E&L** studies.

# Essential Principles

- Informed Selection of Materials of Construction leads to the development of components that are suitable for their intended use.
- Informed Selection of Components leads to the development of systems that are suitable for their intended use.
- Proper Assessment of Systems, simplified via the use of intentionally selected materials and components, establishes that the systems are suited for their intended use.

Characterization, Hazard Identification; USP <661.1>

Qualification, Risk Assessment; USP 661.2

# Materials – USP <661.1>

**Objective:** Material Characterization (Hazard Identification)

**Purpose:** Enable material selection

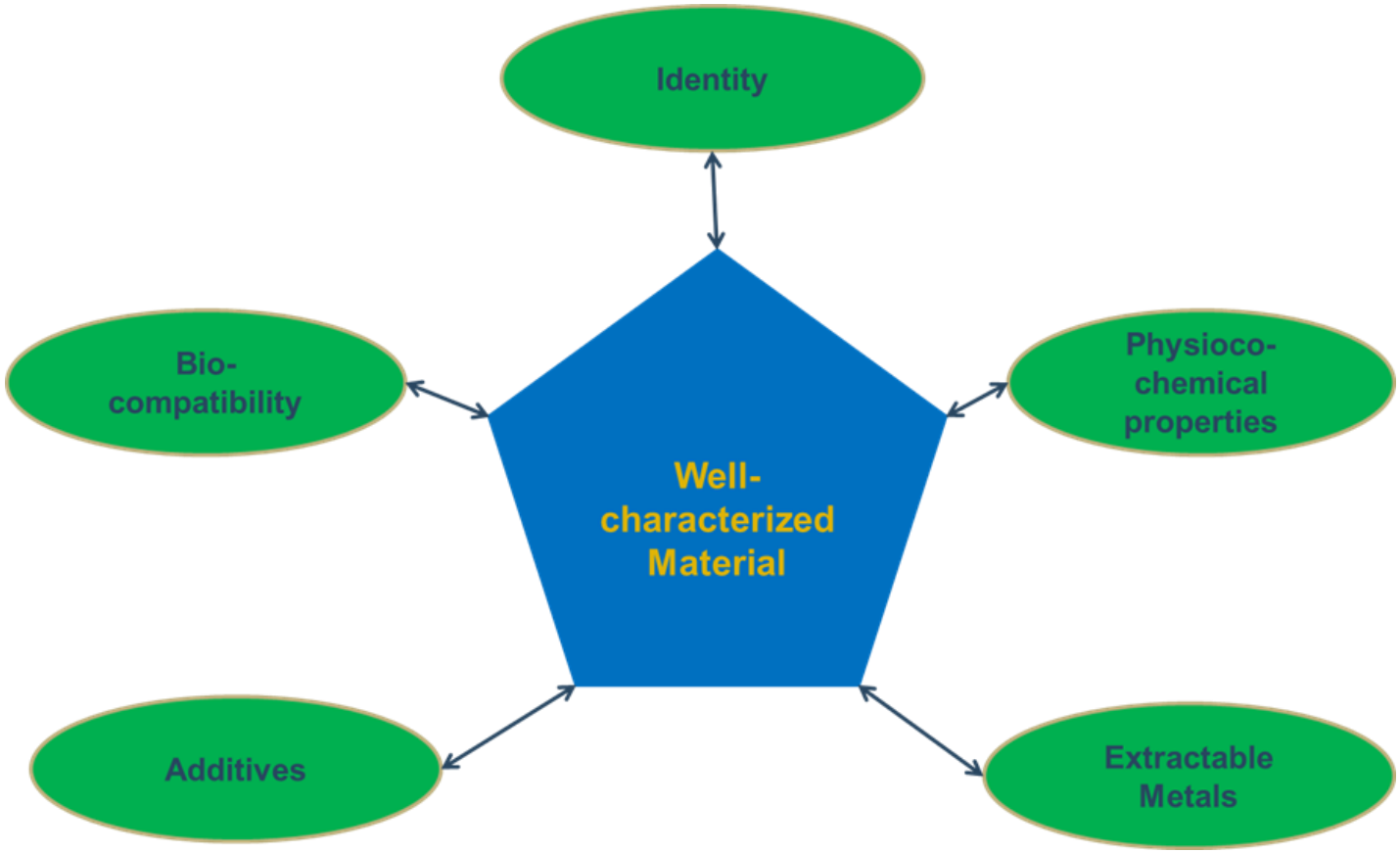
**Value:** Material characterization data drives selection

## Contents

- Identity
- Biocompatibility[1]
- Physicochemical testing (water extracts)
- Extractable Metals (as appropriate)
- Polymer Additives[1]

[1]The specific tests and specifications for these parameters vary in terms of the dosage form and the material.

# A Well-Characterized Material



# Application of Tests, <661.1>

| Table 1. Application of Tests | | |
|---|---|---|
| **Test Parameter** | **Oral and Topical Dosage Forms[a]** | **All Other Dosage Forms** |
| Identification | X | X |
| **Physicochemical** | | |
| UV Absorbance | X | X |
| Acidity/Alkalinity | X | X |
| Total Organic Carbon (TOC) | X | X |
| Extractable Elements | ---[b] | ---[b] |
| Plastic Additives | ---[c] | X |
| **Biological Reactivity** | | |
| In vitro per *Biological Reactivity Tests, In Vitro ⟨87⟩*[d] | --- | X |

[a] For aqueous-based oral drug products that contain cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), additional extractables information may be needed to determine suitability. If additional information is required, perform Plastic additives tests.

[b] As deemed necessary and appropriate by end-user. See USP ⟨1661⟩ for additional information.

[c] Provide reference to the Indirect Food Additive regulations in 21 CFR 174–186, specifically those addressing the purity criteria and limitations pertaining to use.

[d] Biological reactivity testing in support of plastic packaging materials used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities.

# Two Important Points about <661.1>

**EXTRACTABLE ELEMENTS:** Because of this, **it is challenging to provide universally effective and efficient tests methodologies, lists of target elements and reporting requirements. It is the material user's responsibility to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished,** taking into account extraction conditions, target elements, and reporting requirement.


**BIOLOGICAL REACTIVITY TESTING** in support of plastic packaging materials used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provides baseline information and **will often not be sufficient to assess the final suitability for use expectations of regulatory authorities**. Thus, it is important to **work with the appropriate regulatory authority** for guidance regarding a product specific application.

# Outcomes of <661.1> Testing

- If a material has been tested per <661.1>, conforms to the reporting requirements in <661.1> and meets the specifications contained in <661.1>, then the material is well-characterized.
- Armed with the test results, a potential user of the material can make and justify the decision whether to use the material in a specific application.
- <661.1> provides information from which suitability for use can be inferred.
- **A material is not qualified by <661.1> testing, the material is characterized by the user's interpretation of the <661.1> data.**

**Selection:** The action of carefully choosing someone or something as being the best or most suitable.

**Qualification:** The action of proving and documenting that a system is suited for its intended use.

# Materials Covered by <661.1>

- **Polyvinyl Chloride, plasticized**
- **Polyethylene**
- **Cyclic Olefins**
- **Polypropylene**
- **Polyethylene Terephthalate**
- **Polyethylene Terephthalate G**
- Polybutylene terephthalate
- **Polyamide (Nylon)**
- Polyurethane
- **Polyethylene vinyl acetate (EVA)**
- Acrylonitrile butadiene styrene
- *Silicones*
- Polytetrafluoroethylene
- **Polycarbonate**
- Polystyrene
- Poly(methyl methacrylate)
- Polysulfone
- Poly(vinylidene chloride)
- **Polyvinyl chloride, unplasticized**

**Bold** = published in current Chapter. *Italics* = found in USP <668> (under development)

# Double Jeopardy?


**Individual plastic materials of construction are deemed to be well characterized and appropriate for use** if:

1. They meet the requirements in this chapter, or
2. **They are used in a packaging system that meets the requirements in *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.**

# Plastic Packaging, USP <661.2>

**Objective:** System Qualification (Risk Assessment)

**Purpose:** Secure regulatory approval of the packaging system or packaged product.

**Value:** Regulatory approval requires system qualification

## Contents

- Characterized materials (per <661.1)>
- Biocompatibility
- Physicochemical testing (water extracts)
- Extractable (and/or leachables) profiling followed by toxicological assessment.

# Dimensions of Safe Packaging

# <661.2> Testing

| Table 1. Application of Tests | | |
|---|---|---|
| **Test Parameter** | **Oral and Topical Dosage Forms[a]** | **All Other Dosage Forms** |
| **Physicochemical** | | |
| UV Absorbance | X | X |
| Acidity/Alkalinity | X[b] | X[b] |
| Total Organic Carbon (TOC) | X | X |
| Appearance of Solution | X | X |
| Total terephthaloyl moieties | PET and PETG only[c] | PET and PETG only[c] |
| Ethylene glycol | PET and PETG only[c] | PET and PETG only[c] |
| **Biological Reactivity** | | |
| *Biological Reactivity Tests, In Vitro (87)*[d] | --- | X |
| **Chemical Suitability for Use** | | |
| Assessment | Risk-based testing | Risk-based testing |
| **Functionality** | | |
| Spectral Transmission | If light protection is necessary | If light protection is necessary |

[a] For aqueous-based oral drug products that contain cosolvents (or if, for any reason, the drug product is expected to extract greater amounts of substances from plastic packaging components than water), additional extractables information may be needed to determine suitability.

[b] Conduct the test for *Acidity* or *alkalinity* only when packaging systems are intended to hold a liquid product or a product that is dissolved in its container before use.

[c] Polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG).

[d] Biological reactivity testing in support of plastic packaging components and systems used for final pharmaceutical product packaging/delivery systems provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities.

# Extractables and Leachables in <661.2>

- An appropriate and rigorous suitability for use assessment may include extractables testing of the packaging component/system and leachables testing of the packaged drug product.
- The design of the extractables and leachables study should be based on sound and justifiable scientific principles, and the studies themselves should be consistent with
  - the nature of both the packaging system and packaged drug product,
  - the clinical use of the packaged drug product, and
  - the perceived safety risk associated with the packaging system and dosage form.
- The nature and degree of testing should be dosage form-dependent and consistent with a risk-based approach.
- General essential principles and demonstrated best-practices recommendations for extractable and leachable studies can be found in:
  - Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1663⟩,
  - Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1664⟩.

# Outcomes: <661.1> & <661.2> Testing

**The packaging component or system is chemically suited for its intended use if:**

- The packaging component or system is constructed from well-characterized materials as defined in ⟨661.1⟩.
- The packaging component’s or system's general physicochemical properties have been established.
- The packaging component’s or system's biocompatibility (biological reactivity) has been appropriately established.
- The packaging component or system has been established to be suitable by means of the appropriate chemical suitability for use assessment.

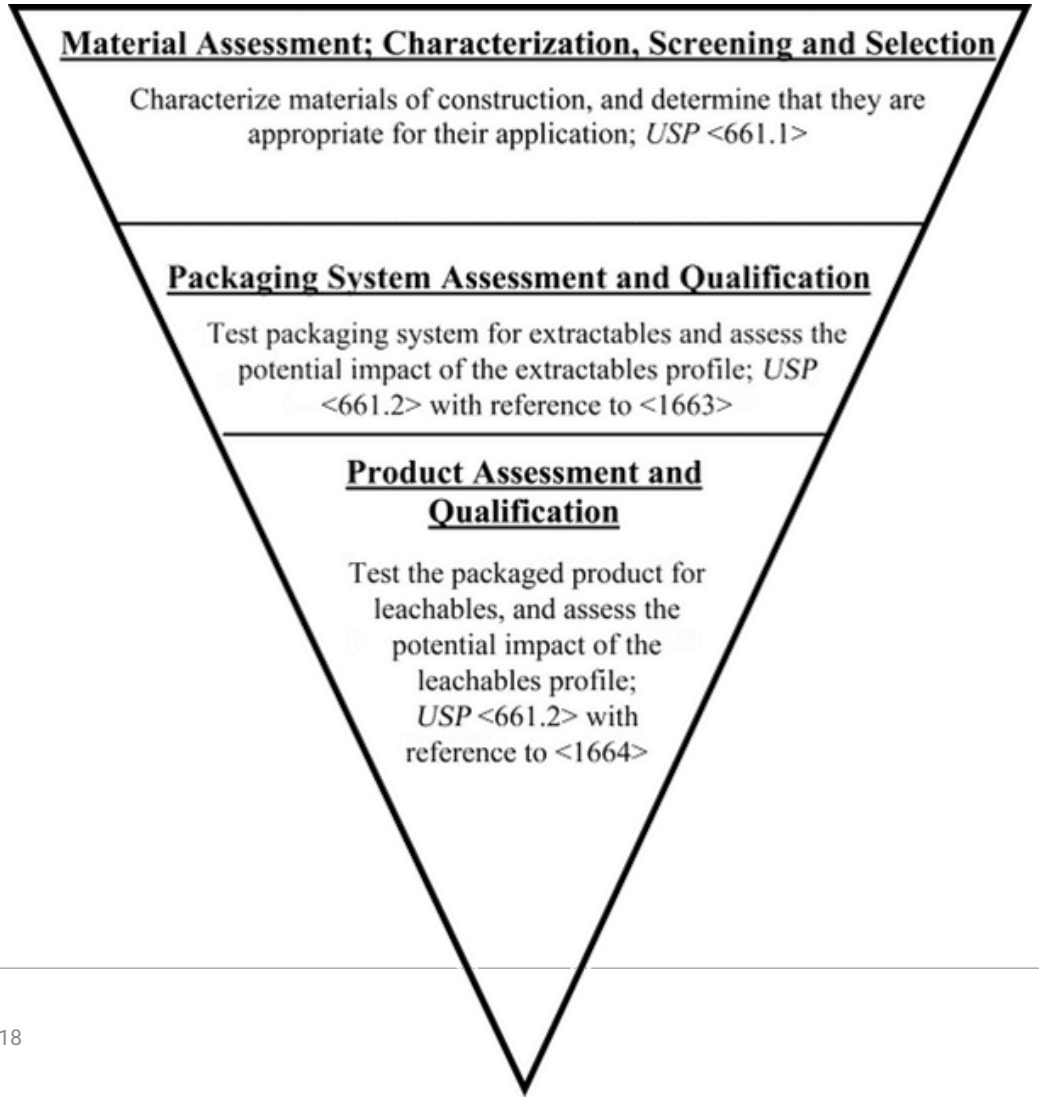
# The “User’s Manual”, <1661>

## Evaluation of Plastic Packaging Systems for Pharmaceutical Use and Their Materials of Construction

1. INTRODUCTION
2. SCOPE
3. GENERAL PRINCIPLES – THE OVERALL ASSESSMENT PROCESS
4. MATERIALS ASSESSMENT: CHARACTERIZATION, SCREENING, AND SELECTION, USP ⟨661.1⟩
5. PACKAGING SYSTEM ASSESSMENT AND QUALIFICATION, USP ⟨661.2⟩
   - 5.1 Extractables and Leachables
6. APPLICABILITY AND APPLICATION OF ⟨661.1⟩
   - 6.1 Applicability
   - 6.2 Application
   - 6.3 Description of Plastics Contained in ⟨661.1⟩
7. APPLICABILITY AND APPLICATION OF ⟨661.2⟩
   - 7.1 Applicability
   - 7.2 Application

**Official as of 1-Nov-2020**

# Three Stage Qualification per <1661>



# Extractables – USP <1663>

## Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

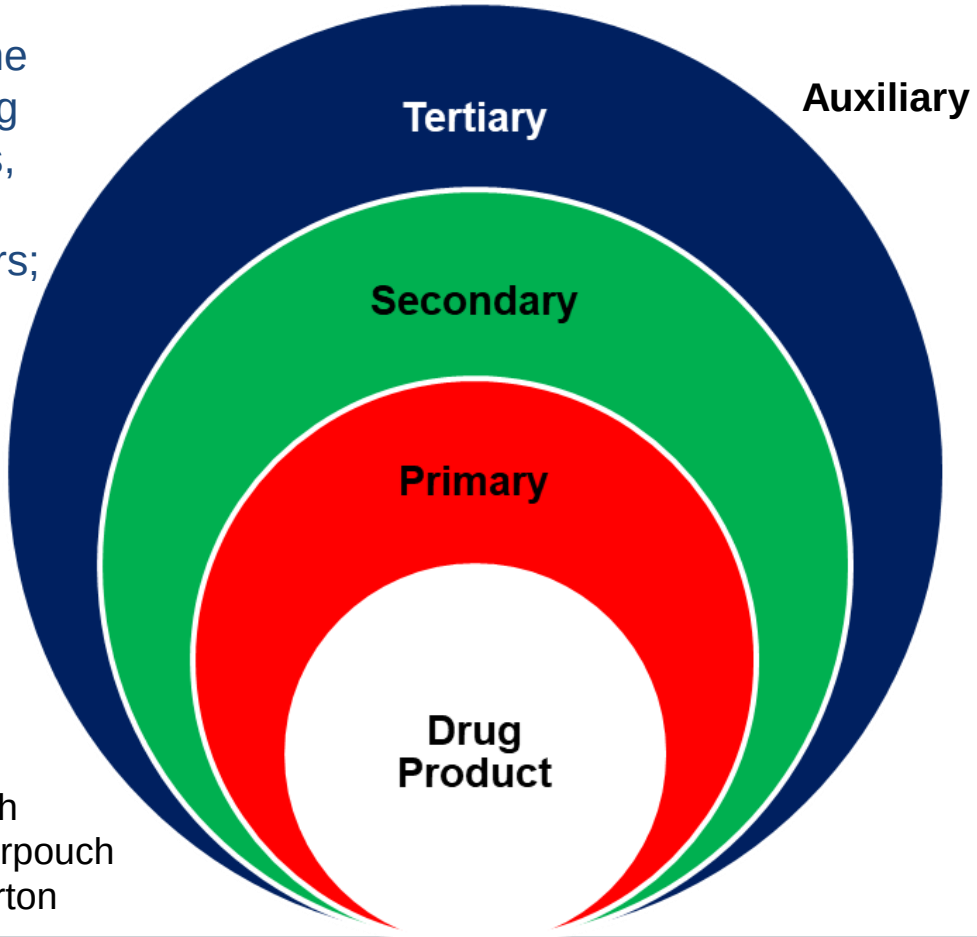
**Official as of 1-Dec-2020**

**Extractables: organic and inorganic chemical entities that are released** from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and **into an extraction solvent under laboratory conditions**. Depending on the specific purpose of the extraction study these laboratory conditions (e.g., solvent, temperature, stoichiometry, etc.) may accelerate or exaggerate the normal conditions of storage and use for a packaged dosage form. Extractables themselves, or substances derived from extractables, have the potential to leach into a drug product under normal conditions of storage and use and thus become leachables.

**Leachables: foreign** organic and inorganic **chemical entities** that are **present in a packaged drug product because they have leached** into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction **under normal conditions of storage and use or during accelerated drug product stability studies**.

# A Hierarchy of Packaging

**Packaging Component:** any single part of the package or container–closure system including the container (e.g., ampules, prefilled syringes, vials, bottles); closures (e.g., screw caps, stoppers); ferrules and overseals; closure liners; inner seals; administration ports; overwraps; administration accessories; labels; cardboard boxes; and shrink wrap.




**Examples:**

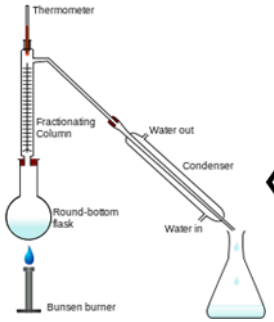
Primary = Bag
Secondary = Overpouch
Tertiary = Label on Overpouch
Auxiliary = Shipping carton

# Extraction Studies - Purposes

**The extraction study should be designed so that it fulfills the study's purpose!**

- Compositionally characterize packaging systems, packaging components, and/or materials of construction
- Assisting in the selection of components and materials of construction
- Establish the affects of various manufacturing processes (e.g., sterilization) on composition
- **Establish the worst-case potential leachables profile**
- Establish the actual leachables profile when it is not scientifically possible to establish actual leachables
- Facilitate qualitative and quantitative leachables–extractables correlations
- Facilitate the development of extractables specifications and acceptance criteria
- Facilitate investigations into the origin(s) of identified leachables

# Two Elements of an Extraction Study




**Generating the Extract**

**Testing the Extract**

# Generating the Extract

**The means by which an extraction process is accomplished are reflected in the juxtaposition of several experimental parameters including:**

- The chemical nature of the extracting media
- The time duration of the extraction process
- The temperature and pressure at which the extraction is performed
- The stoichiometry of the extraction process (extracted surface area per unit volume of extracting solution)
- The mechanism or process by which the extraction is accomplished

**Extraction processes should allow completion in a reasonable time frame but should not be so aggressive that they alter the qualitative and/or quantitative nature of the resulting extractables profile.**

# Extraction Techniques

- ***Maceration (solvent soaking)***—the test article is allowed to soak for a period of tie in an organic or aqueous extracting solvent at temperatures below the solvent's boiling point. Analysts can also fill packaging system units with extracting solvent and store them at relevant temperatures.
- ***Reflux***—the test article is immersed in boiling solvent for a period of time.
- ***Soxhlet***—the test article is placed in the “thimble” of a Soxhlet extraction apparatus that is slowly filled with redistilled solvent from a boiling flask/condenser system; and periodically, the extracting solvent (containing extractables) is siphoned back into the boiling flask and the process begins again (for as many times as required to attain equilibrium).
- ***Sealed vessel***—the test article and extracting solvent are sealed inside a container and heated for a period of time.
- ***Instrument-based solvent extraction***—the test article is placed inside a sealed apparatus and extracted in an automated cycle; examples include pressurized fluid extraction, microwave-assisted extraction, and supercritical fluid extraction.
- ***Sonication***—the test article and extracting solvent are placed into an extraction vessel and immersed in solvent inside an ultrasonic bath.





[1]R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.

# Testing the Extract

1. **Scouting:** analytical techniques that provide information regarding bulk chemical properties of organic and/or inorganic chemical entities present in an extract which can be used to guide extractables discovery, identification, and quantitation For example; TOC, UV, delta pH, NVR.
2. **Discovery:** testing an extract to produce analytical results (signals) that are attributable to individual extractables
3. **Identification:** the process by which the molecular structure of an unknown analyte is elucidated from compound-specific analytical data.
   - Unknown
   - Partial
   - Tentative
   - Confident
   - Confirmed
4. **Quantitation:** the process of establishing (estimating) the concentration of an extractable in an extract.
   - Qualitative (estimate)
   - Semi-quantitative
   - Quantitative

# General Recommendations per <1663>

- **Generation of extracts should be accomplished with:**
  - Multiple solvents or extracting media with varying extracting power based on the known extracting power of the drug product vehicle;
  - Multiple and complementary extraction techniques, including those with the capability for volatiles analysis;
  - Extraction conditions that allow equilibrium to be achieved.
- **Characterization of extracts should use:**
  - Multiple and complementary analytical techniques;
  - Careful sample preparation, keeping the analytical technique(s) in mind;
  - A systematic process for identification and quantitation of extractables.

# Leachables – USP <1664>

## ASSESSMENT OF DRUG PRODUCT LEACHABLES ASSOCIATED WITH PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS

**Official as of 1-Dec-2020**

This chapter covers various important concepts, including:

1) the requirement for leachables studies;
2) fundamental concepts for leachables studies;
3) thresholds for leachables and their application;
4) The design and implementation of leachables studies;
5) leachables method development and validation;
6) Extractables/leachables correlations
7) leachables specifications, including acceptance criteria.

# Leachables Studies

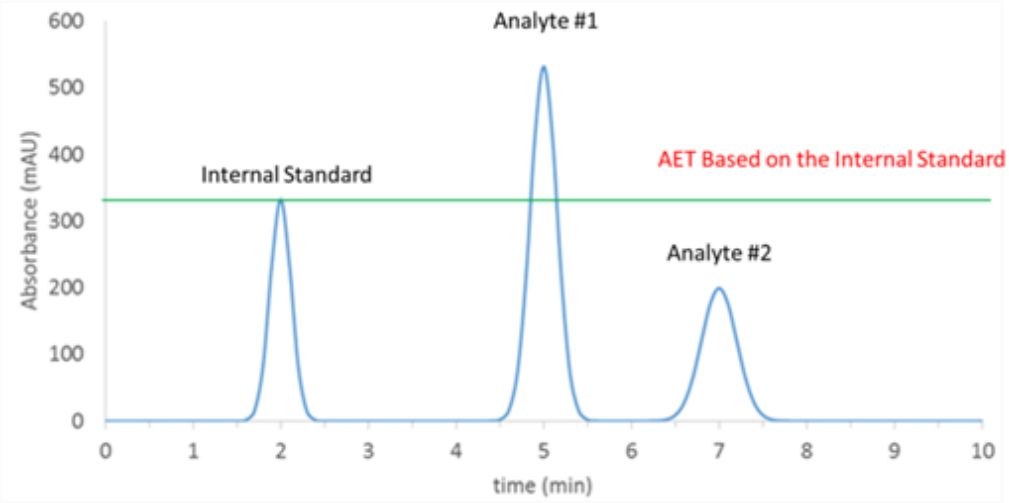
- A leachables study is a laboratory investigation (to establish) qualitative and quantitative leachables profile(s) over the proposed shelf-life.
- The purpose of a leachables study is to systematically and rationally identify and quantify drug product leachables to the extent practicable, and within certain defined analytical threshold parameters.
- The results of leachables studies are used to understand the impact of leachables on patient safety and drug product quality and stability.

# Safety Thresholds

**Safety thresholds are important in leachables assessment because reporting and risk assessing every individual leachable at the limits of current analytical technology is neither necessary, from a toxicological perspective, nor feasible.**

**Safety thresholds allow for a science- and risk-based determination of acceptable levels of leachables.**

**The analytical evaluation threshold (AET) establishes which leachables should be reported for safety evaluation and qualification.**




R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.

# Validation of Quantitative Methods

**The extent of validation required depends on the goals of the leachables study in which the analytical method is being used.**

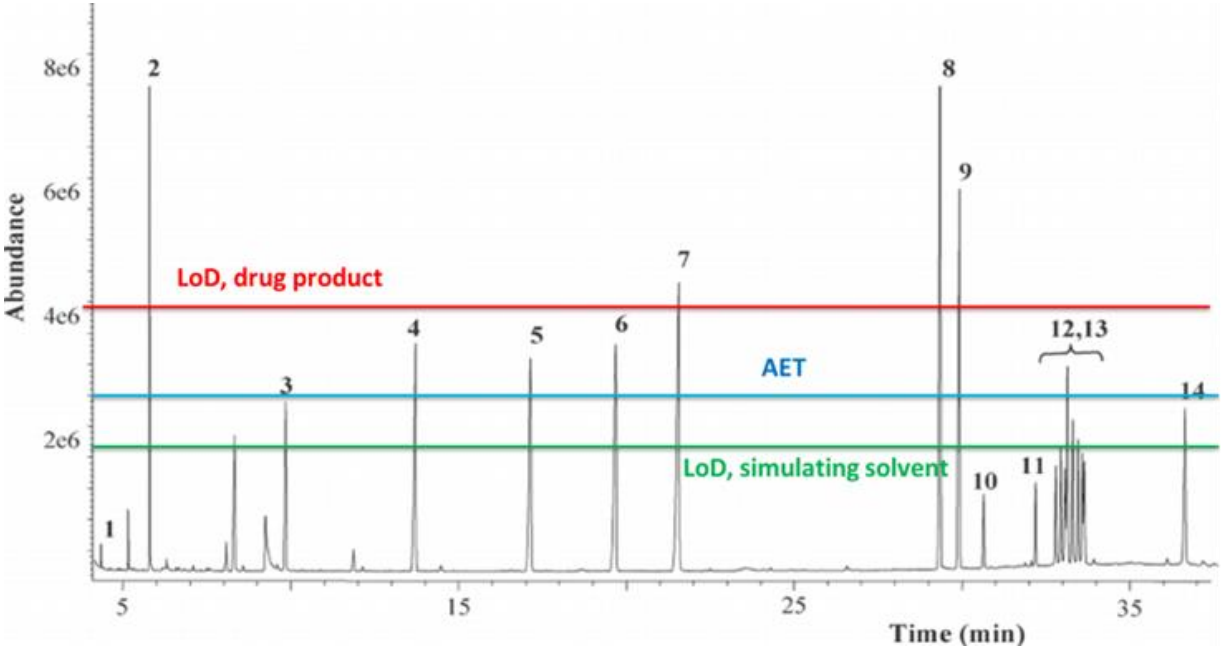
**Validation parameters may include:**

- accuracy,
- precision (repeatability, intermediate precision),
- specificity,
- limit-of-detection, limit-of-quantitation,
- linearity and range, and
- robustness.

**System suitability tests and criteria should also be developed for each leachables method.**

# The Simulation Study

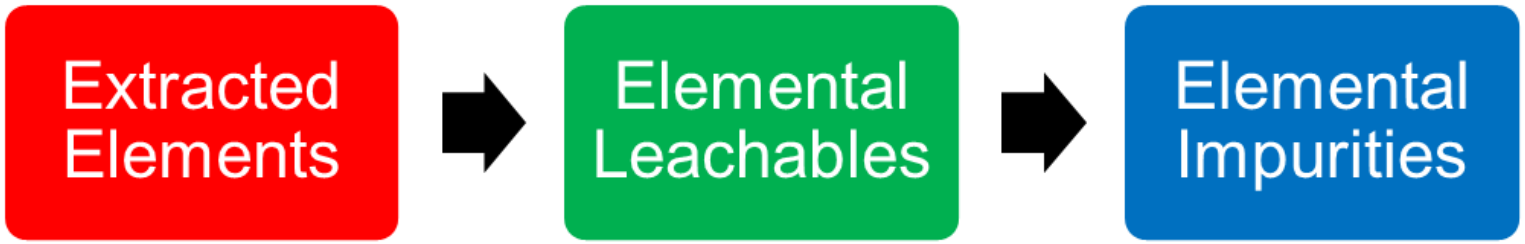
**It is possible that in cases of very low thresholds (e.g., AETs), quantitation of drug product leachables might still not be analytically feasible, even with high sensitivity target compound analytical methods.**




A simulation study simulates the drug product over shelf life but with simulating extraction solvent(s) that are easier to test than the drug product itself.

# Elemental Leachables

The results of extractables testing of plastic packaging systems should be used to establish those elemental impurities that should be monitored as targeted elemental leachables in the drug product.



# Items Used in Pharma Manufacturing

**USP <665> PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS**

**USP <1665> Characterization of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products**

## Current Status

- USP<1665> is official as of 1-May-2022.
- USP <665> was published in USP/NF 2022 but is not official until 01-May-2026.

# <665> - Scope

## In Scope:

- Biological Drug Substances and Biological and Non-biological Drug Products
- ("Traditional") Pharmaceuticals, "Small Molecule" Drug Products, Biologics (pharmaceuticals produced by a biological process such as recombinant proteins expressed in cell culture, antibody-drug conjugates (ADCs) and products used in cell and gene therapy)
- Single-Use Systems and Multi-Use Systems

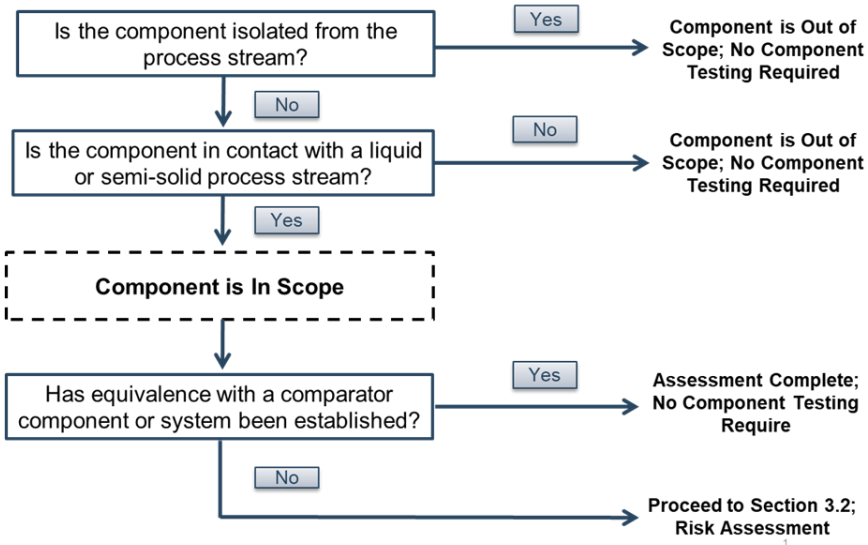
## Out of Scope:

- Non-biological Drug Substances
- Auxiliary items (Scoops, funnels, pipettes, graduated cylinders, weighing dishes, beakers, etc.)
- Solid or gaseous process streams
- Rubber (elastomeric) components

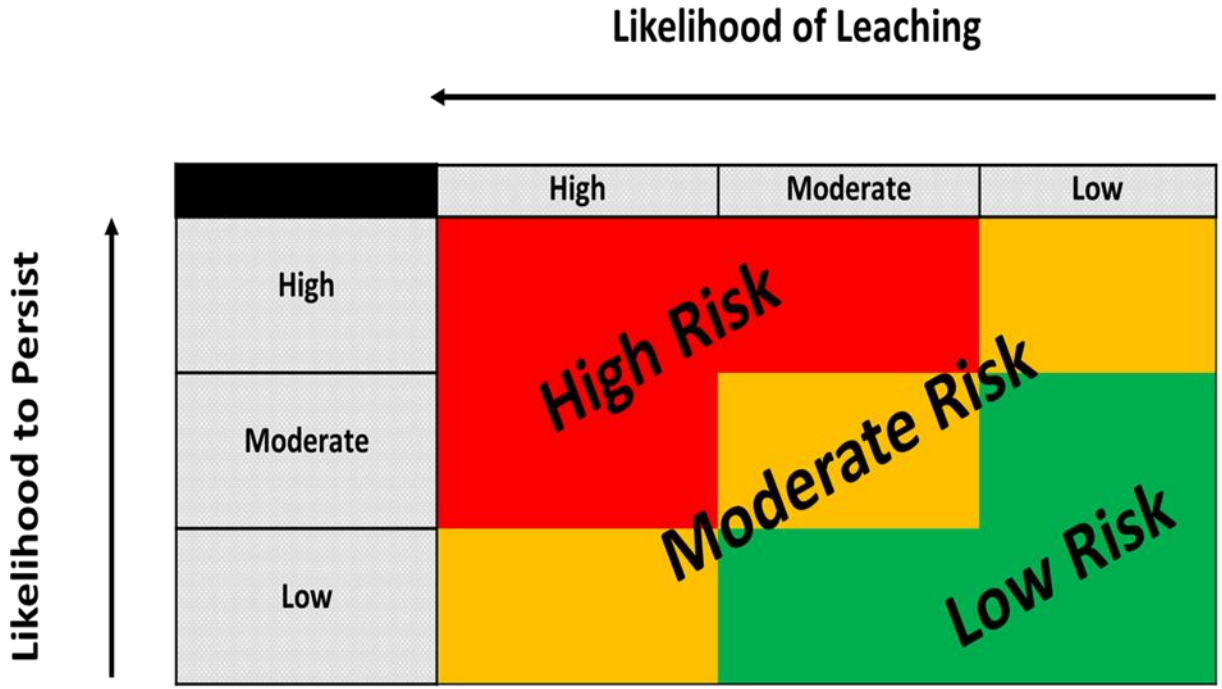
# <665> Decision Process


**Is testing required?** **What is the leachables risk?** **What testing is required?**

**Initial Assessment:**



# <665> Risk Assessment




**<665> does not specify a mandatory Risk Evaluation Matrix.** Rather, **it is the responsibility of the sponsors to establish and justify their own Matrices.** An example Matrix is contained in USP <1665>.

# Required Risk Dimensions

**The Risk Evaluation Matrix must address the following considerations:**

1. The material's or component's "propensity to be leached",
2. The process stream's "leaching power",
3. The "driving force" for leaching (contact conditions),
4. Elimination or dilution of PERLs from the process stream by upstream process steps,
5. The inherent safety risk associated with the manufactured drug product.

The outcome of any risk assessment process (including the use of a Risk Evaluation Matrix) must be one of three risk categories, **low** risk, **moderate** risk and **high** risk.

# Required Testing per <665>

**Table 2. Guidelines for Application of Chemical Component Tests as Established by Risk**

| Risk Level | Extraction Solutions for Chemical Testing[a] | Chemical Testing of Extracts |
|---|---|---|
| Low | *Solution C1* | • Non-volatile residue<br>• UV absorbance |
| Moderate | *Solution C1* | • Organic extractables profiling |
| High | *Solution C1*<br>*Solution C2*<br>*Solution C3* | • Organic extractables profiling<br>• Extracted elements (as necessary and appropriate)[b] |

**Solution Composition:**

C1 = 50/50 Ethanol/water
C2 = Salt solution, pH 3.0
C3 = Phosphate buffer, pH 10

# Extraction Conditions per <665>

| Component | Extraction Solutions | Extraction Conditions at 40°C | | | |
|---|---|---|---|---|---|
| | | 1 Day | 7 Days | 21 Days | 70 Days |
| Containers intended for storage | All | X | | X | X |
| Containers not intended for storage[b] | All | X | | X | |
| Tubing attached to containers not used for storage | All | | | | |
| Tubing attached to containers used for storage | All | X | | X | X |
| Tubing for fluid transport[c] | All | X | | X | |
| Connector/Disconnector[a] | All | X | | X | |
| Aseptic Connector/Disconnector | All | X | X | | |
| Small components (o-rings, gaskets, check valves, diaphragms, septa, polymer pump surfaces, sensors | All | X | | | |
| Ports on container not used for storage | All | X | | X | |
| Ports on containers used for storage | All | X | | X | X |
| Closures (e.g., molded stoppers) for storage containers | All | X | | X | X |
| Filters (process, sterilizing and virus) | All | X | X | | |
| Filtration Cassettes (Tangential Flow) | All | X | | | |
| Tangential flow modules for perfusion or continuous processing | All | X | X | X | |
| Impellers and molded parts for bioreactors and mixers [b] | All | X | | X | |
| Filling Needle | All | X | | | |
| Chromatography column housing | All | X | | | |

Red = USP <665>  X = BPOG protocol

Footnotes a, b and c talk to circumstances where longer or shorter extractions may be appropriate.

# Acceptance Criteria

**A low risk component that is deemed to be qualified for use if:**

- The tests specified for low risk components (UV absorbance, NVR, delta pH) have been performed
- The test results have been reviewed in the context of whether the risk classification is corroborated or not.

**A moderate or high risk component is deemed to be qualified for use if:**

- The extractables profile has been toxicologically safety risk assessed.
- The toxicological safety risk assessment concludes that the probable risk posed by all extractables is within acceptable parameters.

# Alternate Qualification Procedures

**Alternative chemical qualification procedures and acceptance criteria may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority. Chapters <1663> and <1664>, applicable to pharmaceutical packaging/delivery systems, may be helpful resources for designing and justifying rigorous and appropriate studies by establishing general essential principles and demonstrated best-practice recommendations for extractables and leachable studies and assessments.**

## Alternate extractions are allowed when extraction conditions:

- Cannot be satisfied (e.g., the surface area to solution volume ratio cannot be achieved).
- Lead to a situation where requirements for extraction cannot be met (e.g. the extraction conditions produce greater then 20% extraction solvent loss)
- Produce a clearly compromised extract (e.g., excessive cloudiness or coloration, particulate matter, etc.).
- Produce a clearly compromised test article (e.g., test article dissolved, distorted and otherwise rendered non-functional).

# Ongoing Work with USP Monographs of Interest:

- USP <661.2> contains a TOC test (water extraction). The means for performing this test and the acceptance criterion for this test are being re-evaluated.
- USP <1663> and <1664> are within their review cycle and will be revised to be consistent with ICH Q3E and current practice.
- USP <660> is currently be revised to add guidance on extractables testing (primarily elemental extractables).
- A new Chapter, USP <662> METAL PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION is in the initial stages of development.
- Substantive revisions to the Biological Reactivity Chapters <87>, <88>, and <1031> are ongoing. The most current versions appeared for public comment in *Pharmaceopeial Forum*, Volume 49(2).

# Ongoing Work Outside of USP:

- ICH Q3E:  May see the Draft Standard for Public Comment in Q4 of 2023
- ISO 10993:18(2020):  Working groups have been established to produce Technical Reports for topics such as:
  - Proper Identification Practices
  - Proper Quantitation Practices
  - Establishing and Managing the AET
  - Recovery Expectations when Extracts are Manipulated Prior to Instrumental Analysis
  - How to Recognize and Deal with Compromised Extracts

# Q&A

## Thank you!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